Division of Dockets Management (HFA-305)
Food And Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

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Comments from the Keep Antibiotics Working Coalition in response to
the Food and Drug Administration's Draft Guidance Document for Industry (#166)
Environmental Impact Assessments (EIA's) for
Veterinary Medical Products (VMP's) - Phase 2(VICH GL38)

May 20, 2004

Keep Antibiotics Working: The Campaign to End Antibiotics Overuse (KAW), is a coalition of health, consumer, agricultural, environmental, humane and other advocacy groups with more than nine million members dedicated to eliminating a major cause of antibiotic resistance: the inappropriate use of antibiotics in food animals. KAW appreciates this opportunity to comment upon the Food and Drug Administration's (FDA) Draft Guidance Document for Industry (#166) Environmental Impact Assessments (EIA's) for Veterinary Medical Products (VMP's) - Phase 2 (VICH GL38), hereafter referred to as the draft guidance.

Recent research has revealed the need for greater scrutiny of the environmental impacts of antibiotics and other antimicrobials as used in both humans and animals (1). The United States Geological Survey (USGS) recently published the results of a national reconnaissance of United States surface waters and found that 80 percent of streams sampled had contaminants associated with animal or human waste water (2). In this study, more than 10 antimicrobials were found in the surface waters sampled including two antimicrobials detected at over one part per billion. Other recent research has found

antibiotic resistance genes in soil microorganisms and ground water impacted by swine waste lagoons (3). These findings clearly indicate that the impacts of antimicrobials on the environment must be considered during the approval process of these veterinary medical drugs.

While the exact quantity of antimicrobials sold in the U.S. is not publicly available, published estimates agree that the bulk of these marketed are used in animal agriculture (4). Most farm animals raised in the U.S. receive antimicrobials both for disease treatment and, in the absence of disease, for growth promotion and disease prevention (5). While antimicrobial use for disease treatment may be limited to individual sick animals for a short duration, antimicrobials used for growth promotion and disease prevention are generally used for large numbers of animals over long periods of time. Antimicrobials administered to animals are largely excreted in active forms. Given the billions of livestock raised in the US each year and the large quantities of antimicrobials administered to these animals, animal agriculture has the potential to release huge quantities of these drugs into the environment. Indeed, by some estimates, more than 24 million pounds of antimicrobials are used annually for nontherapeutic purposes in swine, poultry, and beef cattle (4).

The draft guidance does not adequately address the potential environmental impacts of antimicrobial VMP's. Antimicrobials used in animals can impact the environment in two ways. First, excreted antimicrobials and their metabolites may enter the environment at high enough concentrations to alter microbial populations and select for resistance in

these organisms. Secondly, antimicrobial use in animal agricultural may select for resistant bacteria at the farm or fish enclosure. These bacteria will then be released into the environment where they can be an environmental hazard themselves and/or they can transfer resistance genes to other organisms. These two mechanisms do not work in isolation. Resistance genes selected on farm prior to release may be maintained in the environment by the presence of antimicrobials subsequently released from farms. Resistant bacteria released into the environment can cause shifts in microbial populations disturbing ecosystems at their most basic level and may also lead to the spread of resistance in pathogens affecting humans and domestic animals. The potential for both of these negative impacts must be considered when considering the environmental impacts of antimicrobial VMP's.

The draft guidance considers the antimicrobial impacts of VMP's in two ways: 1) through the nitrogen transformation tests as part of the recommended terrestrial effects studies, and 2) through the acknowledgement that some regulatory authorities prefer blue-green algae as the target in freshwater algal growth inhibition studies. Neither of these recommended studies comes close to adequately addressing the potential impacts of antimicrobials on the environment.

The approach of the draft guidance is to examine a predicted environmental concentration (PEC) of the VMP being considered along with its metabolites. This approach is inadequate for antimicrobials because it ignores the potential for antimicrobial use to result in the introduction to the environment of resistance determinants. The draft

guidance is also flawed in that it recommends only very limited testing of the antimicrobial activity at the PEC through the nitrogen transformation studies and by mentioning the possibility of examining the impact on blue green algae in freshwater aquatic systems. These types of studies do not begin to address the most likely impacts of antimicrobial VMP's on the environment. KAW recommends that the guidance expand the species considered for impact tests to better match the likely effects of the VMP under consideration. In addition, the proposed EIA's should take into consideration not only the release of the VMP but also the impact of the high levels of antibiotic resistant bacteria released in the waste in both the aquatic and terrestrial branches.

KAW recommends that tier A and B tests be included that would assure that 1) the VMP use would not result in the release of drug resistance determinants into either terrestrial or aquatic ecosystems and that 2) the PEC is low enough that it would not inhibit bacterial growth or select for resistance in either soil or water bacteria. EIA's for antimicrobial drugs that do not include these studies to determine the impact of VMP's on microbial populations are misguided and will miss the most likely adverse effects of these drugs on the environment.

KAW appreciates the opportunity to comment on the draft guidance and strongly encourages the guidance be modified to consider the most likely effects of antimicrobials on the microbial ecosystem.

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(1) Kümmerer, K. 2003. Significance of antibiotics in the environment. Journal of Antimicrobial Chemotherapy 52, 5-7

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(3) Chee-Sanford, J. et al, 2001. Occurrence and Diversity of Tetracycline Resistance Genes in Lagoons and Groundwater Underlying Two Swine Production Facilities. Applied and Environmental Microbiology 67(4):1494-1502.

(4) Union of Concerned Scientists, 2001. Hogging It!: Estimates of Antimicrobial Abuse in Livestock. http://www.ucsusa.org/food_and_environment/antibiotic_resistance/page.cfm?pageID=264

(5) McEwen, S. and Fedorka-Cray, 2002. Antimicrobial Use and Resistance in Animals. Clinical Infectious Diseases 34(Supplement 3):S93-106.

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Sincerely,

Steven Roach
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Food Animal Concerns Trust